Current testing requirements for donors of human cells and tissues

Preventing Organ and Tissue Allograft-Transmitted Infection: Priorities for Public Health Intervention

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Donor Eligibility and RCDADs

- Donor Eligibility rule defines relevant communicable disease agents or diseases (RCDADs); establishments must screen and/or test for RCDADs
- Defined in 1271.3(r) – (1) lists particular RCDADs and (2) describes when communicable disease agents or diseases may be added to the list of RCDADs – in order to allow additions based on emerging infectious diseases
- Additions to the "list" of RCDADs would be added through guidance (draft, public comment, then finalize, except in cases of public health emergency)

RCDADs

- For all HCT/Ps
  - HIV, types 1 and 2
  - HBV
  - HCV
  - Human TSE, including CJD
  - Treponema pallidum (agent of syphilis)
- For viable, leukocyte-rich HCT/Ps
  - HTLV, types I and II
- For reproductive HCT/Ps
  - Chlamydia trachomatis
  - Neisseria gonorrhea

Additional RCDADs

- The donor eligibility draft guidance adds new RCDADs according to definition in § 1271.3(r)(2) (published May 2004; not finalized)
- "FDA believes that the following meet the standards for identification of relevant communicable disease agent"—
  - West Nile Virus
  - Sepsis
  - Vaccinia (Smallpox vaccination)
  - Severe Acute Respiratory Syndrome (SARS)

Donor Testing - General

- Donor testing must be performed at lab
  - Registered with FDA
  - CLIA certified or CMS equivalent
- Donor tests
  - FDA-licensed, approved, or cleared donor SCREENING tests (not diagnostic)
  - Used in accordance with the PI
  - Should be labeled for use for cadaveric donors if such a test is available
  - Recommendations may change with time and increasing technology

Donor Testing - General

- Interpretation of test results
  - ONLY according to manufacturer’s instructions in the PI
  - Triplicate testing is NOT recommended in any manufacturer's test kit instructions
- Specimen collection should be at same time as, or within 7 days before or after, collection of the cells or tissues with certain exceptions
- Donors who have had transfusions or infusions 48 hours prior to specimen collection should be evaluated for plasma dilution or excluded (algorithm included in guidance)

Screening vs Diagnostic test kits

- Clinical trials to support donor screening test kits perform testing in a “pre-screened”, low-prevalence population (emphasis on sensitivity)
- Clinical trials to support diagnostic test kits generally perform testing in a symptomatic population with suspicion of having a particular disease before the test is performed (more emphasis on specificity)
- Performance of a test kit in a low-prevalence population (pre-screened donors) is therefore not known for diagnostic test kits
- FDA believes that tests specifically labeled for use for donor screening are the best tests to use in any donor screening situation

Donor Testing

- Specifically recommended tests include FDA licensed (or cleared) screening tests for
  - HIV types 1 and 2 – anti-HIV-1 *and* anti-HIV-2 or licensed combination test
  - HBV – HBsAg *and* anti-HBcore (total=IgG+IgM)
  - HCV – anti-HCV
  - *Treponema pallidum* serological test for syphilis (Donor with reactive non-Treponemal screening test and nonreactive specific Treponemal confirmatory test is permitted to donate)

Donor Testing

- Additional screening tests for viable, leukocyte-rich cells or tissue
  - HTLV types I and II – FDA-licensed anti-HTLV I/II
  - CMV – not RCDAD, but must test, using FDA-cleared screening test for anti-CMV.
- Additional tests for genitourinary diseases for donors of reproductive cells and tissues
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhea*
  - Currently no FDA-licensed, approved, or cleared donor *screening* tests for either.

NAT and Donor Testing

- DE Draft Guidance published before any NATs were approved for use in cadaveric specimens; at that time only HIV and HCV were licensed for use in blood donor (or other living donors) screening
- Draft guidance states “As more information becomes available, FDA may recommend these tests for use in cadaveric tissue donors.”
- “FDA does recommend that living donors of HCT/Ps (e.g., hematopoietic stem/progenitor cell donors, semen donors) be tested with FDA-licensed NAT blood donor screening tests for HIV and HCV.”

Currently Licensed NAT test kits for donor screening

- Gen-Probe/Chiron – Procleix HIV-1/HCV Nucleic Acid Test (TMA) [B, P, L/O, C]
- National Genetics Institute – UltraQual HIV-1 RT-PCR & HCV RT-PCR Assays [P]
- Roche Molecular Systems – COBAS AmpliScreen HIV-1 & HCV Assays (PCR) [B, P, L/O, C]; HBV Assay (PCR) [B, P]
- B – Blood P – Plasma L/O - Living and Organ donors C - Cadaveric

NAT Donor Screening in the Pipeline*

- WNV – Gen-Probe [B, P, L/O, C]; Roche Molecular Systems [B, P]; GP also has BLA under consideration
- HBV – Gen-Probe has HBV as part of multiplex test under consideration for BLA at this time [B, P, L/O, C]; RMS has HBV NAT cadaveric indication under consideration for BLA at this time

* Publicly available information, with knowledge of manufacturer

Cadaveric indication

- FDA considers cadaveric specimens to be different than living blood donor specimens; additional validation studies must be performed
- Claims may be obtained as an additional claim (or supplement on already approved test kits) for test kits with an indication for use in screening blood donors
- Guidance published November 2004 “Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)”
- FDA works with industry to encourage development of test kits for use in cadaveric donors

Cadaveric Indication

- Notable issues with HCT/P specimens
  - No validation of testing after long term specimen storage (this would be very helpful to the HCT/P industry)
  - Claims for HCT/P donors may only use ID testing and not be pooled testing unless separate validation is performed (none to date)
  - Turnaround time is often an issue with cadaveric HCT/Ps – corneas are released in <7 days
  - It is helpful to have claims for both serum and plasma for cadaveric donors because of limited specimen volume

Organ and "other living donors"

- "…is intended for use as a donor screening test to detect [HIV-1 RNA] in plasma samples from individual human donors, including donors of Whole Blood and blood components, Source Plasma and other living donors. It is also intended for use to screen organ donors when specimens are obtained while the donor's heart is still beating. This test is not intended for use on specimens from cadaveric (non-heart-beating) donors. This test is not intended for use on samples of cord blood. This test is not intended for use as an aid in diagnosis."
- The organ/other living donor claim does not require data submission; ID testing only

Organ donor testing

- FDA does not regulate organ donors; nor do we decide what screening and testing should be performed for organ donors
- The risk/benefit ratio for HCT/Ps and organs is different – as such, the screening and testing requirements are different
- Further information is contained in the OPTN policies at: http://optn.org/PoliciesandBylaws/policies/pdfs/policy_2.pdf

Further Information

- Cadaveric guidance located at http://www.fda.gov/cber/gdlns/cadbldhctp.pdf
- Cadaveric claims are jointly reviewed by OCTGT and OBRR
- All tissue related publications can be found at http://www.fda.gov/cber/tissue/docs.htm

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